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June 22, 2000

David Ross, M.D.
Food and Drug Administration
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Dear David:

I am writing in regards to our recent conversation regarding the Draft Guidance entitled – Catheter-Related Bloodstream Infections – Developing Antimicrobial Drugs for Treatment. As I mentioned to you in our conversation, unfortunately, I had not become aware of the document until just recently. I have reviewed the document and have some minor suggestions.

Page 5 – In the third bullet, second sentence, I would suggest changing the beginning of the second sentence to ≥ 3:1 ratio . . . in other words, the ratio should be at least 3:1 but not limited to this ratio or 5:1. In fact, the higher the ratio, the greater the sensitivity. According to the article by Siegman – Igra, et al., *Journal of Clinical Microbiology*, April 1997, ≥ 3:1, ≥ 4:1, > 5:1, have sensitivities of 83%, 94% and 100%, respectively. All were 100% specific for the diagnosis of catheter-related bloodstream infection.

Page 9 – In the first bullet, I would make changes as noted above. More and more data is accumulating regarding the sensitivity and specificity of the differential time to positivity in a diagnosis of catheter-related bloodstream infection (see Farr, B. *Lancet*, 2000). At least with catheters in place for a more prolonged period of time (e.g. ≥ 2 weeks) this technique appears to be quite sensitive and specific and could easily be adapted by most hospitals in the U.S. and abroad since it does not require the same technology as quantitative blood cultures. Consider adding this as criteria in the section entitled – A Blood Culture Aspirated from a Catheter (first bullet).

In the second bullet would replace > than 5 CFU/segment with ≥ 15 CFU/segment

In the third bullet, recommendations are made regarding quantitative cultures of catheter hubs. Unfortunately, a quantitative cut-off has not been clearly established to the best of my knowledge. Dr. Sitges-Serra and colleagues, who first described the importance of the hub as a source of catheter-related bloodstream infection, have not used any particular cut-off in their numerous publications on this subject. This makes sense since a cut-off is more relevant to a catheter-tip culture, in which case the catheter is pulled through the skin and may become contaminated in the process. In

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contradistinction to this, hub cultures should not be associated with skin contamination, and therefore, any concordant growth with isolates obtained from percutaneously-drawn blood cultures would strongly suggest the hub as the source. It should be noted that in studies that I have done with Dr. Maki, in which hub, skin, and catheter-tip cultures were obtained at the time of catheter withdrawal, we found numerous instances where isolates in the blood matched isolates from the hub, and skin. Other investigators have made the same observation. Therefore, many cases of catheter-related bloodstream infection, at least those with relatively short-term (i.e. dwell times of < 2 weeks) are associated with colonization of the hub and skin and it would be difficult, if not impossible, to determine which of the two sites was the most important source of bloodstream infection in those cases.

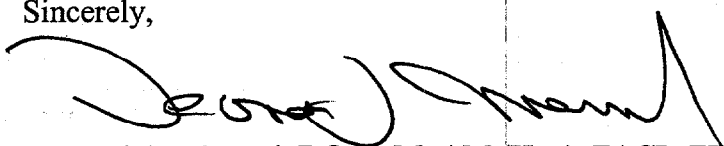
Page 10 – It is unclear to me whether or not the exclusions listed at the top of the page refer to the time of enrolling a patient versus excluding enrolled patients who are found to have complications such as endocarditis. I presume you mean the former. This may be an important distinction and may require further clarification in that it is not uncommon for a patient to respond properly to catheter withdrawal and initiation of antimicrobial therapy such that repeat blood cultures may be negative and fever has resolved, only to find evidence of endocarditis on echocardiogram that was not appreciated based on the patient's signs and symptoms. Therefore, in some studies in which an echocardiogram is not required at the time of catheter-related bloodstream infection and enrollment, it may be difficult to distinguish endocarditis which developed on therapy versus endocarditis which was present at the onset of therapy but was occult.

Page 16 – Reference 13 please correct the spelling of Sitges-Serrra.

I hope the above comments are helpful to you and your colleagues. You should all be proud of yourselves with the excellent and authoritative Draft Guidance. It is very well done and beautifully summarizes a tremendous of volume of information in a terse, yet easy to read fashion.

Please feel free to contact me should you have any questions or concerns regarding the above comments. It has been my pleasure to work with you and I look forward to our future collaboration.

Sincerely,



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